IIV Working Group: National Children's Study

Proposed Core Hypothesis: Altered timing of early childhood immunizations will lead to no increased rate or severity of disease later in life

Final Draft

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I. Proposed core hypothesis question

The National Children's Study (NCS) plans to collect data for a large cohort of very young children followed into adulthood. To be adequately tested, the proposed hypothesis requires the full length and breadth of this prospective study.

The hypothesis is stated as a null hypothesis because the direction of the anticipated effect is not known *a priori*. The general hypothesis is postulated as:

> Ho: Altered timing of early childhood immunizations will lead to no increased rate or severity of disease later in life.

This hypothesis is further specified and operationalized into two sub-hypotheses. These define altered timing as deviation from recommended guidelines (two different sets proposed) during the first three years of the child's life. Also specified is the disease of interest[1].

> 1) Ho: Adherence to the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule[2] for children ages three and under will lead to no change in the onset or severity of diabetes mellitus in children ages 10 and older.
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> 2) Ho: Adherence to the European Academy of Pediatrics (EAP) recommended immunization schedule for children ages three and under will lead to no change in the onset or severity of diabetes mellitus in children ages 10 and older.

II. Workgroup collaboration

We welcome and encourage collaboration with NCS groups, as well as groups outside of the NCS, concerned with issues of maternal and child health, vaccine safety and supply, obesity and nutrition, and chronic illness.

III. Contact person for proposed core hypothesis question

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[1] Diabetes is emphasized here because its expected prevalence is relatively high for a study population of the size planned (100,00 children). The overall hypothesis and approach, however, may be applied equally well to other disease outcomes of interest, such as respiratory disease.

[2] In place at the time the child is subject to childhood immunization exposure – defined here as during the first three years of the child's life.

IV. Public health significance

The hypothesis aims to determine if an association exists between altered timing of immunizations and the development of diabetes mellitus. Other disease outcomes of interest for investigation could be Hib meningitis, poliomyelitis and respiratory infections that could be studied by following a parallel study design. In recent years, diabetes mellitus has seen a sharp overall increase as well as a significant increase in adolescents and young adults.

In 1998, 15.7 million people (6% of the US population) were affected by diabetes. The overall incidence rate is approximately 798,000 per year (CDC National Diabetes Fact Sheet, November 1 1998). The prevalence of diabetes among those under the age of 20 years was 123,000, or about 0.16% of all people in this age group. The prevalence rate for those 20 years or older is 15.6 million (8.2% of all people in the age group).

The mortality rate of diabetes has also increased over the years from 34,851 deaths in 1980 to 68,399 deaths (3% of US population) in 1999. Of the total diabetes related deaths reported in 1999, 104 (0.6%) deaths were reported in the 20-24 year age group, 582 (1.4%) in the 25-34 year age group, and 1142 (2.2%) in the 35-44 year age group (Health, United States, 2001).

Diabetes can lead to a variety of extremely debilitating complications. The complications of diabetes include heart disease, stroke, high blood pressure, blindness, kidney disease, nervous system disease, amputations, dental disease and complications of pregnancy:

> Heart disease is the leading cause of diabetes-related deaths; adults with diabetes have heart disease death rates 2-4 times higher than adults without diabetes. The risk of stroke is 2-4 times higher in people with diabetes, while an estimated 60-65% of people with diabetes have high blood pressure.
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> Diabetes has been found to be the leading cause of new cases of blindness in adults 20-74 years of age, and diabetic retinopathy in 12,000–24,000 new cases of blindness each year. Diabetes is also the leading cause of end-stage renal disease, accounting for about 40% of new cases.
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> About 60-70% of people with diabetes have mild to severe forms of nervous system damage which often includes impaired sensation or pain in the feet or hands, slowed digestion, carpel tunnel syndrome and other nerve problems. Severe forms of diabetic nerve disease are a major contributing cause of lower extremity amputations. More than half of lower limb amputations occur among people with diabetes. From 1993-1995, about 67,000 amputations were performed each year among people with diabetes.
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> Periodontal disease has been reported to occur among 30% of people aged 19 and over with Type I diabetes. The newborn death rate for pregnant women with diabetes is 3-5% in comparison to 1.5% in women who do not have diabetes. The

rate of congenital malformations in babies born to women with diabetes varies from 0-5% in women with prenatal case, to 10% in women with no prenatal care (CDC National Diabetes Fact Sheet, November 1, 1998).

The total direct and indirect cost of diabetes was $98 billion in 1997. This figure included a $44 billion cost of direct medical care and a $54 billion indirect cost related to disability, work loss, and premature mortality (CDC, 1998).

Diabetes-related complications may cause severe burden not only to individuals but also family members and their communities due to loss of work, premature death and additional health care costs. The study of diabetes in the NCS cohort could lead to findings that help establish strong guidelines for the prevention of diabetes, thereby preventing premature morbidity and mortality, especially in adolescents and young adults.

V. Justification for a large, prospective, longitudinal study

A sufficiently large cohort, widely diverse, with consistent, reliable long-term follow-up for serious health outcomes at least into adolescence would offer numerous opportunities to explore vaccine safety related questions.

The annual US birth cohort exposed to universal vaccination is approximately 4 million infants. With advancements from older vaccine types to newer (e.g., live attenuated or inactivated poliovirus vaccine), alterations in adjuvants (e.g., thimerasol), and other innovations, new vaccines can be recommended for universal use in that annual birth cohort. The vaccine effects are not often carefully explored with respect to relatively rare (<1:1000) short-term adverse events, longer-term adverse events (such as type 1 diabetes mellitus, multiple sclerosis, poliomyelitis), or in diverse subsets of infants not previously evaluated.

The introduction of combination vaccines and of multiple concurrent immunizations further complicates evaluation and separation of individual vaccine effects. Vaccine manufacturers and public health agencies are well aware of these limitations, and are working to address these critical safety questions. There are feasibility, economic and risk:benefit considerations that make much larger comparative clinical trials prior to vaccine licensure and universal use highly unlikely for every new vaccine. Even existing post-marketing safety evaluation systems, such as the CDC Vaccine Datalink, lack the ability to follow children for many years. "Vaccination risks range from common, minor and local adverse events to rare, severe and life-threatening conditions.

Thus, recommendations for immunization practices balance scientific evidence of benefits for each person and to society against the potential costs and risks of vaccination programs." [MMWR CDC Surveillance Summary 2002 Feb 8; 51 (RR-2): 1-35] Yet the safety questions persist. The scope and duration of the National Children's Study will permit numerous vaccine safety questions to be addressed.

VI. Scientific merit

The available comparative information at the time of vaccine licensure and introduction to the general population is limited by the duration of vaccine development, such that the only adverse events observed occur within a few years of vaccination. Further, this information is limited by the homogeneity of the subjects involved in vaccine trials.

The question of adherence to the ACIP recommended schedule for childhood vaccination is the first of many vaccine safety related questions to be addressed. If the null hypothesis in this case is not rejected, public health officials would not have to focus resources at maximizing that adherence and could use those resources to address other opportunities, e.g. maximizing vaccination coverage. If those children who received immunizations following the ACIP recommendations had demonstrably fewer serious adverse events, the rationale for parents to ensure adherence to the recommended schedule, and even to the use of immunization registries [HHS Immunization and infectious diseases (Goals 14-26) In: *Healthy People 2010*, vol. 1], would be based even more strongly on the health benefits to their infant, and less on the school enrollment requirements or other rationale. Investigating further could offer alternatives when the supply of vaccines is affected making it impossible to adhere to the recommended schedule.

The Institute of Medicine, in its recently issued Immunization Safety Review (2001) and in several vaccine safety workshops, has called for the evaluation of longer term outcomes. "According to workshop participants, these findings reinforce the need for long term studies to determine late-onset adverse effects of vaccines." [Vaccine Safety Forum: Summary of Two Workshops (1997)] A cohort of 100,000 represents 2.5% of the annual birth cohort, and follow-up of decades represented approximately ten times the usual duration of post-vaccination follow-up. The National Children's Study affords an invaluable opportunity to evaluate vaccine safety in a much more heterogeneous cohort, and for observation of longer term outcomes than has previously been available.

VII. Potential for innovative research

The National Children's Study provides the potential to incorporate or react to new vaccine developments that may occur during the exposure period of those children enrolled, such as edible vaccines (e.g., bananas or tomatoes). Depending upon the timing and geographic introduction of such new vaccines, those receiving and not receiving the new vaccines could be compared and contrasted. Genetic analyses may provide links, as yet unknown, that identify individuals predisposed to diabetes or other health outcomes. The range of potential pioneering research that might impact the cohort enrolled could be limitless.

VIII. Feasibility

Critical period for exposure and outcomes – The critical period for exposure to childhood immunizations is defined as the period between birth and three years of age, when receipt of recommended immunizations should be complete.

Sampling needs – The CDC estimates a diabetes prevalence of about 123,000 cases per year for people under the age of 20. Testing of the proposed hypothesis would thus require the full cohort of NCS participants. With the introduction of new vaccines there may be a need for over-sampling of special population subgroups (e.g., Hispanics, Native Americans).

If a new vaccine is introduced into ACIP recommendations during the period of study, specific sub-hypotheses will be proposed for children who had access and potential exposure to the new vaccine.

Number, frequency and timing of study contacts – Initial contact will occur at first enrollment and at the time of the first vaccination. Subsequent contacts will occur after age 3 to collect vaccination histories and other information, and at approximately 5-year intervals thereafter (at the minimum) to test for diabetes symptoms and update medical history and other information.

Measurement tools for assessing exposures or outcomes – No added burden beyond the proposed scope of the NCS is expected to collect vaccination information. Collection of urine and blood samples will be required; some additional urine/blood testing may be needed above what is required in normal well-care practice. Due to heightening concern about obesity, and its predisposition to diabetes, pediatricians and other health professionals are likely to increase the frequency of diabetes diagnostic tests. This helps to justify the level of surveillance and biospecimen collection for the study of the proposed hypothesis, especially where the child has a family history of or personal risk factors for diabetes.

Community involvement – Requires cooperation of parents, teachers, and local health professionals, although this is not expected to pose additional burden beyond the scope of what already is proposed for the NCS.

Other burden to the participant and family associated with this hypothesis -- None expected. If diabetes disease is identified, we could provide referral information for follow-up treatment.